IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
An Educational Conference for People with Multiple Sclerosis
WELCOME

Lauren B. Strober, PhD
Senior Research Scientist, Neuroscience & Neuropsychology
Kessler Foundation

Moyra Rondon, LCSW
Manager, Program Implementation & Engagement
National Multiple Sclerosis Society, New Jersey Metro Chapter
TODAY’S AGENDA

MORNING SESSION
Cognition & MS

AFTERNOON SESSION
Panel Discussion I – Fatigue, motivation & physical activity
Panel Discussion II – Everyday life, employment, wellness & social cognition
Please note...

In your folder you will find:
- Materials pertaining to today’s discussions
- A list of current studies at Kessler Foundation
- A contact sheet (Please hand in at the recruitment table)

For today:
- Please complete questions cards (Hand in before lunch)
- Please stop by our vendors and exhibitors tables
- Parking assistance will be available throughout the day
Please note...

After you leave today:

Podcasts of today’s talks will be available at: Kesslerfoundation.org/MS2017

Look for our follow-up survey
National MS Society-NJ Metro Chapter Highlights

Moyra Rondon, LCSW
Getting to know the National MS Society

The National MS Society is focused on helping people affected by MS live their best lives through connection, support and information, no matter their location, needs or circumstances.

- Founded in 1946 by Sylvia Lawry
- A nationwide network of chapters across the country
- Programs and Services
- Advocacy at the national and state near
- Volunteer engagement opportunities
- Fund-raising events
- Investment in MS research
National MS Society is a driving force of MS Research

- Stop the disease in it’s tracks
- Restore what’s been lost
- End the disease forever

Over 300 projects funded annually and $974 million in research funding to date
What services are available across the Society?

- MS Navigator Services: Information & referrals and link to case management as needed
  Phone: 1-800-344-4867  Email: ContactUsNMSS@nmss.org

- Website and Publications: www.nationalMSsociety.org

- MS online community: MSConnection.org

- Nationwide Core Programs
  - Connections Program: Peers helping Peers
  - Scholarship Program
  - Monthly Tele-learning/webinar
  - Healthcare Access Partnerships
What programs are available locally?

Chapter developed programs:

- Wellness activities
- Locally based education programs
- Local in person self-help groups (30 in NJM)
- Nursing Home Outreach
- Collaborative programs with community partners
- Hispanic Family Day (NYC area)
- African American/Black Families Affected by MS (NYC area)
Coming soon in our area!

• Sign up for Fall Wellness Series
  - free yoga and tai chi classes

• Impact Series 2017 – Sunday, December 3rd
  Join us for our new approach to our annual meeting!
  Register online at nationalMSsociety.org/NJM or call 1-800-344-4867.

• WALK MS: April 28th and 29th 11 sites throughout chapter area.
Getting Involved

ADVOCATE
Spread the word. Make a change.

EDUCATE
Increase awareness. Help others learn about the disease.

PARTICIPATE
Join us for our client programs or annual fundraising events: WALK MS, Bike MS, and Muckfest.

VOLUNTEER
Give your time and talents. Help others by doing what you love.
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
An Educational Conference for People with Multiple Sclerosis
Overview

• Cognitive problems in MS

• Factors that affect cognition

• Impact on everyday life

• Key cognitive problems

• Medication
From Persons with MS

“Appointment after appointment Dr. XXX listened to my complaints, but didn’t take them seriously or relate them to MS. Compared to her patients in wheelchairs, my thinking symptoms must have appeared minor, but they were very powerful, and had the potential to be just as devastating as the physical difficulties”

Gingold (2006) Facing the cognitive challenges of MS, 39
Multiple Sclerosis

- MS is a progressive disease producing widespread:
  - plaques in white matter
  - axonal damage
  - damage to grey matter
- Results in range of symptoms
  - Sensory/motor
  - Fatigue
  - Cognitive
  - Neuropsychiatric
MS - Background

- Affects about 450,000 persons in the US
- Approximately 2.3 million worldwide
- Age of Onset: 20-40 years
- Almost 2 times more frequent in females
- **Etiology** - Unknown, thought to be an autoimmune disease triggered by a viral infection in genetically susceptible individuals
Cognitive experience of patients with MS:

“a marked enfeeblement of the memory; conceptions are formed slowly ...”
MS - Historical

- Early 1900’s saw a great debate on cognition!

- By 1960’s, medical students taught
  - cognitive change not characteristic of MS

- Early 1970’s: cognitive impairment in about 3%

- Today, cognitive impairments up to 65% in MS
From Persons with MS

“I thought I was losing my mind. It was difficult to explain to others what was happening when I didn’t know myself. I do remember the fear and loneliness that went along with all this. I silently begged God, ‘Do what you will to my body, but please leave my mind alone’”

Hall (1999) *Inside MS*, 17, 52-53
What is Cognition?

Dictionary:
“the act or process of knowing”
What is Cognition?

- **Receptive Functions**
  - Sensory input, paying attention, rapid processing incoming information

- **Learning and Memory**
  - Acquiring, storing, retrieving

- **Thinking**
  - Mental organization and manipulation

- **Execution and expressive functions**
  - Acting upon and communicating intentions
Cognitive Deficits in MS

- Information processing speed/efficiency
- Learning and Memory
- Executive functions
  - planning, organization, initiation
- Perceptual processing
- Social cognition
Cognitive Impairment in MS

Chiaravalloti & DeLuca, 2008, *Lancet Neurol*
The frequency of cognitive impairment tends to increase over MS course.

**Figure 1: Cognitive Impairment in Patients with MS from 6 Italian Centers**

- **CIS (n = 167)**: 35%
- **RRMS (n = 759)**: 45%
- **SPMS (n = 74)**: 79%
- **PPMS (n = 40)**: 91%
- **Overall (n = 1040)**: 46%

Amato et al, 2016
Spared Cognition in MS

- Basic Attention

- Essential verbal skills
  - Comprehension
  - Expression
  - Naming
  - Repetition

- Intelligence
## Evolution of Cognitive Impairment in MS over 10 year period

<table>
<thead>
<tr>
<th>Cognitive impairment</th>
<th>Initial Testing</th>
<th>4 year follow-up</th>
<th>10 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>74%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Mild</td>
<td>8%</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>Moderate</td>
<td>18%</td>
<td>16%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Amato et al, (2001), *Archives Neurol*
Some Factors which affect Cognition in MS

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>RR &lt; SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Physical Disability</td>
<td>Not always</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Not well known</td>
</tr>
<tr>
<td>Depression</td>
<td>It may, not always</td>
</tr>
<tr>
<td>Stress</td>
<td>It may, not always</td>
</tr>
<tr>
<td>Gray Matter atrophy</td>
<td>Strong predictor</td>
</tr>
<tr>
<td>Gender</td>
<td>Males at increased risk</td>
</tr>
</tbody>
</table>
Some Factors which Influence Neuropsychological Profiles in MS
Fatigue and Cognition
Subjective Fatigue Across the Workday

Mean Fatigue Score

Fatigue and Cognition
Subjective Fatigue Across the Workday

Mean Fatigue Score

Baseline
End of Day

PASAT Mean Correct

Baseline
End of Day

Some Factors which Influence Neuropsychological Profiles in MS

AMBIENT TEMPERATURE
Association between temperature and cognitive status in MS patients

Leavitt et al., (2012), *Neurology*

**Cross sectional Study**

$r_p = -0.45, p = 0.006$

**Longitudinal Study**

$r_p = -0.39, p = 0.010$
Some Factors which Influence Neuropsychological Profiles in MS
### Table 3: Cognitive test comparisons between MS cannabis users and nonusers

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Cognitive test</th>
<th>Cannabis users, mean (SD)/n (%) impaired</th>
<th>Nonusers, mean (SD)/n (%) impaired</th>
<th>$t$ or $\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Learning and memory</strong></td>
<td>CVLT-II immediate recall</td>
<td>49.5 (10.9)</td>
<td>52.5 (11.2)</td>
<td>$t = -0.969$</td>
<td>0.337</td>
</tr>
<tr>
<td></td>
<td>CVLT-II long delay recall</td>
<td>10.6 (3.6)</td>
<td>11.2 (2.7)</td>
<td>$t = -0.681$</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>BVMT-R total recall</td>
<td>22.1 (8.3)</td>
<td>22.8 (7.6)</td>
<td>$t = -0.284$</td>
<td>0.777</td>
</tr>
<tr>
<td></td>
<td>BVMT-R delayed recall</td>
<td>8.2 (3.1)</td>
<td>8.7 (3.1)</td>
<td>$t = 0.545$</td>
<td>0.588</td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td>COWAT total score</td>
<td>31.0 (11.9)</td>
<td>33.7 (10.8)</td>
<td>$t = -0.845$</td>
<td>0.403</td>
</tr>
<tr>
<td><strong>Visuospatial perception</strong></td>
<td>JLO score$^a$</td>
<td>23.9 (4.7)</td>
<td>26.7 (3.5)</td>
<td>$t = -2.417$</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td>D-KEFS sorting score</td>
<td>8.4 (2.4)</td>
<td>10.3 (2.7)</td>
<td>$t = -2.704$</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>D-KEFS description score</td>
<td>31.4 (9.5)</td>
<td>37.4 (10.4)</td>
<td>$t = -2.127$</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Information processing speed</strong></td>
<td>PASAT 3.0</td>
<td>36.0 (12.0)</td>
<td>44.0 (11.4)</td>
<td>$t = -2.402$</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>PASAT 2.0</td>
<td>26.1 (7.6)</td>
<td>35.0 (11.7)</td>
<td>$t = -3.188$</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>SDMT Total</td>
<td>42.4 (11.4)</td>
<td>50.4 (12.9)</td>
<td>$t = -2.329$</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Global cognitive impairment</strong></td>
<td>≤1.5 SD on 2 or more of 11 cognitive tests, n (%)</td>
<td>16 (64.0)</td>
<td>8 (32.0)</td>
<td>$\chi^2 = 5.128$</td>
<td>0.024</td>
</tr>
</tbody>
</table>

No group differences on psychiatric variable

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Honarmand et al (2011), *Neurology*
“Whatever subjective benefits patients may derive from using street cannabis (e.g., pain and spasticity) should be weighed against the associated cognitive side effects”

Honarmand et al (2011), Neurology, p 1153
Some Factors which Influence Neuropsychological Profiles in MS

CIGARETTE SMOKING
Smoking and Cognition in MS

Cigarette smoking:
• May trigger MS
• Facilitate transformation from CIS to MS
• Increase relapse frequency
• Promote progression of MS

Ozcan et al, (2014), *Neuropsychiatric Disease and Treatment*
Cognitive impairment at time of diagnosis is a good predictor of:
- conversion to definite MS
- disability progression
- transition to secondary progressive MS
- cortical thinning
Change in disability and cortical thinning across groups over 8 years

CN: cognitive normal
mCI: mild cognitive impairment
sCI: severe cognitive impairment
cTh: cortical thinning

Pitteri et al, MSJ, 2016
Cognitive Problems and Everyday Life Functioning

- Cognitive deficits in MS have been shown to negatively affect daily life including:
  - Employment
  - Driving
  - Social and vocational activities
  - Household activities
  - Sexual functioning
  - Family activities
  - Overall QOL
  - Increased psychiatric illness

- **Beyond physical disability alone**

59% not working 5 years post dx

**Figure 4.** Number of years after diagnosis before people with MS stopped working*

*People with MS who are not currently employed

VR-Driving System

Assessing Cognitive Impairment in MS

- Neurologist judgment poorly associated with actual cognitive impairment
  - No greater than chance

- Clinical interview and neurological exam not sufficient

- What about patient self report?

How to Assess Cognition?

• Patient Self report
  – Predicts emotional distress
  – Not objective cognitive impairment

• Neuropsychological Evaluation (gold standard)
  • Correlated with brain imaging
  • Predicts everyday life activity
    – Employment
    – Cooking
    – Driving
    – Internet functional tasks (book airline ticket)
    – Other ADL’s
CMSC Member Survey on Cognitive Screening Practices
Respondents (N=207) to CMSC member survey asking, “How are patients screened for cognitive problems/changes at your practice?” Respondents were instructed to check all that apply.

- 29% formal testing
- 52% not assessed
- 19% self report

Overview

• Cognitive problems in MS
  – Factors affect cognition
  – Impact on Everyday Life

–Key Cognitive problems

• Can we improve cognitive problems?
• Cognitive Reserve and MS
• Exercise
• Medication
Information Processing Efficiency

Processing speed
Working Memory
“Often I have a 5-15 second delay in recognizing what is going on, what is being said, who I am talking to....Don’t ask me a compound question unless you want me to shut down completely. One thing at a time and wait...Up until about a year ago, I thought MS would just be a physical battle”

Gingold (2006) *Facing the cognitive challenges of MS*, 89-90
Speed of Processing Defined

- Amount of time to complete a given amount of work
  OR
- Work completed given a limited amount of time
WM Defined

temporary storage and active maintenance and manipulation of thinking for on-line use

(Baddeley, 2000)
What are the odds or relative risk of having a PS or WM Deficit in MS compared to that of the general population?
# Risk Estimates (Odds Ratios) of PS vs WM impairment in MS

<table>
<thead>
<tr>
<th>All MS vs. Controls</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing Speed Index</td>
<td>10.4</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>2.7</td>
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</table>

<table>
<thead>
<tr>
<th>RRPM vs. Controls</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td>Processing Speed Index</td>
<td>5.3</td>
</tr>
<tr>
<td>Working Memory</td>
<td>1.3</td>
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</table>

<table>
<thead>
<tr>
<th>SMPM vs. Controls</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing Speed Index</td>
<td>65.2</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>9.0</td>
</tr>
</tbody>
</table>

DeLuca et al, *JCEN*, 2004
Summary

Information processing deficit in MS is primarily processing speed and not working memory accuracy.
Learning and Memory
Defining Learning

- **Learning** - “The *process* of acquiring new information”
- **Memory** - “The *persistence* of learning in a state that can be revealed at a later time”
Learning and Memory Process

- Encoding
- Consolidation
- Retrieval

Learning
Identifying the Cause

- Retrieval failure hypothesis?
- Acquisition deficits?

Train subjects to a learning criterion
SRT Trials to Criterion

Trials To Criterion

Recall and Recognition

DeLuca et al., 1994, *J Clin Exp Neuropsych*
Logical Memory: Trials to Criterion

 Logical Memory: Delayed Recall

Paired Associate Learning: Delay Recall

Learning and Memory in MS

• Primary deficit in MS is in the acquisition of information

• Cognitive rehabilitation the focus in improving acquisition/learning
Overview

• Cognitive problems in MS
  – Factors affect cognition
  – Impact on Everyday Life
  – Key Cognitive problems

• Can we improve cognitive problems?
  • Cognitive Reserve and MS
  • Medication
What can we do to improve cognition?

Cognitive Rehabilitation

Learning and Memory
Memory rehabilitation for people with multiple sclerosis (Review)

das Nair R, Martin KJ, Lincoln NB

15 studies
989 persons with MS

Significant effect of memory intervention on:

Objective assessments of immediate and long term follow-up
QOL in immediate follow-up
Cognitive Rehabilitation Studies

63% of all studies

1993-1997
1998-2003
2004-2009
2010-2015

42 total studies
Video Games and Cognitive Rehabilitation

– Can I tell my client to use “brain games” or “video games” for cognitive rehabilitation?

A Consensus on the Brain Training Industry from the Scientific Community

Max-Planck-Institut für Bildungsforschung
Max Planck Institute for Human Development

October 20, 2014

75 Leading Cognitive Psychologists & Cognitive Neuroscientists Representing 48 Universities

“We object to the claim that brain games offer consumers a scientifically grounded avenue to reduce or reverse cognitive decline when there is no compelling scientific evidence to date that they do.”

Lumosity to Pay $2 Million to Settle FTC Deceptive Advertising Charges for Its “Brain Training” Program

• “Lumosity preyed on consumers’ fears about age-related cognitive decline, suggesting their games could stave off memory loss, dementia, and even Alzheimer’s disease. But Lumosity simply did not have the science to back up its ads.”

• Lumosity claimed that training would:
  – 1) improve performance on everyday tasks, in school, at work, and in athletics
  – 2) delay age-related cognitive decline and protect against mild cognitive impairment, dementia, and Alzheimer’s disease
  – 3) reduce cognitive impairment associated with health conditions, including stroke, traumatic brain injury, PTSD, ADHD, the side effects of chemotherapy, and Turner syndrome, and that scientific studies proved these benefits.


Federal Trade Commission Press release, 1/6/2015
Pharmacological Approaches
Pharmacological Approaches

• In principle, DMTs potentially improve cognition
  – approved DMTs reduce T2 & T1 brain lesions
  – some reduce the progression of brain atrophy
  – decrease of inflammatory activity may contribute to better cognitive performance

• Symptomatic drugs may have specific effects

• Review RCT’s
Pharmacological Approaches

• Methodological problems in DMT RCT’s
  – cognition a secondary or even a tertiary outcome
  – explorative outcome often single cognitive test
  – patients’ cognitive status not an entry criterion
  – studies not powered on cognitive parameters
    • not appropriate to detect cognitive changes

• Observational studies on DMT studies
  – vast majority are non-randomized
  – small samples with different clinical characteristics
  – heterogeneous cognitive assessment tools and outcome measures

• Results must be viewed with caution
Pharmacology and Cognition in MS

No Support: 13
Support: 7
## Pharmacology and Cognition in MS

<table>
<thead>
<tr>
<th>Category</th>
<th>Support</th>
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</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>1 of 3</td>
</tr>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td>2 of 6</td>
</tr>
<tr>
<td>L-amphetamine</td>
<td>2 of 3</td>
</tr>
<tr>
<td>Other agents</td>
<td>2 of 8</td>
</tr>
</tbody>
</table>
Overall Summary

• Cognitive impairment in 2/3 persons with MS
• PS and learning & memory primary problems
• Significantly affects everyday life activities
  – Work with your clinicians to get assessed
• Rehabilitation can improve cognitive symptoms
  – Its time MS patients get treated
• Can we build a cognitive reserve?
• Exercise
• Medication
THANK YOU

Acknowledgments

Nancy Chiaravalloti, Ph.D.
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Nancy Moore, M.S.
Helen Genova, Ph.D.
Victoria Leavitt, Ph.D.
Ekaterina Dobryakova, Ph.D.
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
An Educational Conference for People with Multiple Sclerosis
Cognitive Rehabilitation

Nancy D. Chiaravalloti, PhD

Director of Neuroscience and Neuropsychology
Kessler Foundation
Research Professor, Physical Medicine and Rehabilitation
Rutgers-New Jersey Medical School
OUTLINE

• The Literature

• Other ongoing work at Kessler Foundation
  – Processing Speed
  – Executive Functioning
    • Wonderkins
The Literature

- Recent Systematic Review (2017)
  - Examined CR literature by cognitive domain
  - Since 2007 – substantial progress

<table>
<thead>
<tr>
<th>Domain</th>
<th># of studies</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Attention</td>
<td>3 studies</td>
<td>1 practice standard; 1 option</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>15 studies</td>
<td>1 practice standard; 4 options</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>4 studies</td>
<td></td>
</tr>
<tr>
<td>Executive Functions</td>
<td>2 studies</td>
<td></td>
</tr>
<tr>
<td>Non-specific &amp; Multiple</td>
<td>14 studies</td>
<td>1 practice guideline</td>
</tr>
<tr>
<td>Metacognition</td>
<td>2 studies</td>
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</tbody>
</table>
The Literature

• Recent Systematic Review (2017)
  – Examined CR literature by cognitive domain
  – Since 2007 – substantial progress

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<td>1 practice guideline*</td>
</tr>
<tr>
<td>Metacognition</td>
<td>2 studies</td>
<td></td>
</tr>
</tbody>
</table>

* Same treatment protocol
Attention

3 studies | 1 practice standard: APT
1 option: RehaCom
Attention

Attention Process Training (APT)
APT Group:

Increase on 3 tests requiring attention
<table>
<thead>
<tr>
<th>3 studies</th>
<th>1 practice standard: APT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 option: RehaCom</td>
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</tbody>
</table>
Attention

RehaCom

Multiple modules available

practice option for treating attention
practice guideline for other cognitive domains
(executive functioning)
RehaCom

Increased activation post-treatment during an attention task in RehaCom group.
## Learning and Memory

<table>
<thead>
<tr>
<th>15 studies</th>
<th>1 practice standard: mSMT</th>
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</thead>
<tbody>
<tr>
<td>4 options:</td>
<td></td>
</tr>
<tr>
<td>• Imagery (basis of mSMT)</td>
<td></td>
</tr>
<tr>
<td>• Music</td>
<td></td>
</tr>
<tr>
<td>• Self-generation</td>
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</table>
Learning and Memory

mSMT
Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial†

Nancy D Chiaravalloti*, 1, 2, 3, John DeLuca1, 2, 3, Nancy B Moore2 and Joseph H Ricker2, 3

1Kessler Medical Rehabilitation Research and Education Corporation, 1193 Pleasant Valley Way, West Orange, NJ 07052, USA; 2UMDNJ-New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ, USA; 3UMDNJ-New Jersey Medical School, Department of Neurosciences, Newark, NJ, USA

ARTICLES

An RCT to treat learning impairment in multiple sclerosis
The MEMREHAB trial

ABSTRACT

Objective: To examine the efficacy of the modified Story Memory Technique (mSMT), a 10-session behavioral intervention teaching context and imagery to facilitate learning, to improve learning and memory abilities in persons with multiple sclerosis (MS).

Methods: This double-blind, placebo-controlled, randomized clinical trial included 86 participants...
Can context and imagery facilitate learning?

- **Memory Retraining Treatment Protocol**
  - Randomized Control Trial
  - Modified Story Memory Technique (mSMT)
  - 10 sessions
    - 2 times per week for 5 weeks
    - 30 to 90 minutes in duration

- **Does it work?**
  - Assessments before and after treatment
  - Neuropsychological assessment, neuroimaging, assessment of daily life
Learning by Group

CVLT Learning Trials

Trial 1 Trial 2 Trial 3 Trial 4 Trial 5

Treatment Control

Kessler Foundation
Everyday Life Self-Report
FAMS General Contentment

Subscale Total Score

Baseline Immediate Follow-Up

(p<.05)

Treatment Control
Family Report of Daily Life
FrSBe Total Score, Family Form

*lower score indicates less symptoms
Changes on Functional MRI Scans

Before and After mSMT treatment

fMRI shows increased activity after treatment only in areas underlying the treated function.

*Treatment Group use more visual areas after treatment.
mSMT Long-Term Effects

CVLT Performance

- Pre
- Post
- 6 months

- control group mean
- treatment group mean

- $z = 1$

Occipital Gyrus

- MTL
- MFG

- $x = -4$
**Learning and Memory**

<table>
<thead>
<tr>
<th>15 studies</th>
<th>1 practice standard: mSMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 options:</td>
</tr>
<tr>
<td></td>
<td>• Imagery (basis of mSMT)</td>
</tr>
<tr>
<td></td>
<td>• <strong>Music</strong></td>
</tr>
<tr>
<td></td>
<td>• Self-generation</td>
</tr>
<tr>
<td></td>
<td>• Spaced trials</td>
</tr>
</tbody>
</table>
Learning and Memory

Music

2 studies by same group
Music mnemonics aid verbal memory and induce learning – related brain plasticity in multiple sclerosis

Michael H. Thaut¹ *, David A. Peterson²,³, Gerald C. McIntosh⁴ and Volker Hoemberg⁵

¹ Center for Biomedical Research in Music, Colorado State University, Fort Collins, CO, USA
² Computational Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, CA, USA
³ Institute for Neural Computation, University of California San Diego, La Jolla, CA, USA
⁴ Department of Neurology, University of Colorado Health, Fort Collins, CO, USA
⁵ Department of Neurology, SRH Rehabilitation Hospital Bad Wimpfen, Bad Wimpfen, Germany

**Spoken vs sung list of words.**

Sung: recalled more word and had more frontal activity

Main effect due to group (F(1,2) = 4.51, p=0.038) [2-way ANOVA]
Learning and Memory

15 studies

1 practice standard: mSMT
4 options:
  • Imagery (basis of mSMT)
  • Music
  • Self-generation
  • Spaced trials
Learning and Memory

Self-generation & Spaced Learning

STEM
Strategy-based Treatment to Enhance Memory (STEM)

- Teaches persons and significant others how to apply novel techniques in daily life

- Teaching application of:
  - Generation effect
  - Spacing effect
  - Testing effect

- 8 session treatment protocol for:
  - Persons with MS
  - Significant Other
STEM Results

Perceived Deficits

Baseline | Follow-up
---|---
Treatment | 8 | 7
Control | 7 | 6

Quality of Life

Baseline | Follow-up
---|---
Treatment | 17.5 | 15.5
Control | 15 | 14

Kessler Foundation

Graphs showing the change in perceived deficits and quality of life over baseline and follow-up for treatment and control groups.
OUTLINE

• The Literature

• Other ongoing work at Kessler Foundation
  – Processing Speed
  – Executive Functioning
    • Wonderkins
Speed of Processing Training

- 10 session computerized PS treatment
  - Laptop administration
  - Highly manualized
  - Used extensively in normal aging

- 3 levels: 1) single discrimination
  2) discrimination task with peripheral target
  3) discrimination task with peripheral target embedded among distractors
Speed of Processing Training

RESULTS

Processing Speed (Coding)

Memory (CVLT)
Speed of Processing Training

RESULTS

Daily Living (TIADL)

[Graph showing comparison between baseline and follow-up in Daily Living (TIADL) for TX and CTL groups]

baseline  follow-up
TX  CTL
OUTLINE

• The Literature

• Other ongoing work at Kessler Foundation
  – Processing Speed
  – Executive Functioning
    • Wonderkins
Wonderworks: More engaging Cog Rehab?

Development grant....

Uses Virtual Reality to make cognitive rehabilitation more engaging

Focuses on executive functioning
- Task switching
- Multitasking
Virtual Reality & Cognitive Rehab

Task Switching

Multi-tasking

Task Switching

Multi-tasking

KESSLER FOUNDATION
Collaborators

John DeLuca, PhD
Yael Goverover, PhD
Glenn Wylie, D.Phil
Ekaterina Dobryakova, PhD
Helen Genova, PhD

Lauren Strober, PhD
Denise Krch, PhD
Silvana Costa, PhD
Nancy Moore, MA
Angela Smith, MA
Funding Sources
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
An Educational Conference for People with Multiple Sclerosis
Staying Cognitively Active

John DeLuca, PhD, ABPP

Senior Vice President for Research
Kessler Foundation
Professor, Physical Medicine and Rehabilitation
Rutgers-New Jersey Medical School
Overview

• Can we keep mentally fit?
• What is cognitive reserve
• Cognitive Reserve in MS
• Brain reserve
• Exercise & Cognition
Frank Lloyd Wright
Started designing the Guggenheim Museum at age 76, completed at age 89

Goethe finished his masterpiece “Faust” at age 81

Galileo published his last paper at age 74, when life expectancy was 35
The Alzheimer’s Association Website

Keep your brain active every day:

- Stay curious and involved — commit to lifelong learning
- Read, write, work crossword or other puzzles
- Attend lectures and plays
- Enroll in courses at your local adult education center, community college or other community group
- Play games
- Garden
- Try memory exercises
Cognitive training: Introduction
What is cognitive training?

- Guided practice on set of tasks related to memory, attention, or other brain functions
- Uses repetitive exercises for a single cognitive ability (e.g., memory) or multiple abilities (e.g., memory and reasoning)
- May be computer-assisted or delivered in person to an individual or small groups
- Based on idea of brain plasticity
- NOT just puzzles or “brain games”
Growth of cognitive training studies

Walton et al. (2014)
Why cognitive training in aging is important

- 65+ population is growing
  - 20% of population (72 million) by 2030

- Cognitive decline is most feared aspect of growing older

- Cognitive impairments heavily affect aging population
  - 1 in 4 adults 70 years or older have an impairment without dementia
  - About 5.3 million people in the U.S. have Alzheimer's disease

Drug trial results are disappointing
Health priorities in older adults

Persons mentioning that this problem is a priority (%)

Memory
Diabetes problems
Osteoporosis
Pain control
Stroke
Cardiac diseases
Colon cancer
Breast cancer

This problem is a priority

This problem is addressed by my physician

Older women’s health priorities and perceptions of care delivery: results of the WOW health survey

N= 2161 older Canadian women
Evidence from the ACTIVE Trial:

Advanced Cognitive Training for Independent and Vital Elderly
ACTIVE Interventions: Common Structural Features

- Small-groups (3-5 participants per group)
- Led by a certified trainer with a scripted manual
- 10 sessions over a 6-week period
- 60-75 minutes per session
- Pre-specified order of sessions and rules for make-ups
- 80% compliance for successful completion
Initial Effect Sizes *(JAMA 2002)*

**Expected Decline**

**Training Gains**

- Memory
- Reasoning
- Speed
10-year trajectory of memory, reasoning, and speed, by training group (*JAGS 2014*)

**Memory**

![Memory graph]

**Reasoning**

![Reasoning graph]

**Speed**

![Speed graph]

*Scores were reversed to graphically present decline.*
10-year trajectory of self-reported IADL difficulty, by training group (JAGS 2014)

* Scores were reversed to graphically present decline.
Secondary outcomes related to everyday functioning: Findings at 5-, 10-yr follow-up

- Mobility and Driving
  - Reduction in Auto Crashes: Speed & Reasoning Training

- Internal Control
  - Increase in Control Beliefs: Speed & Reasoning Training

- Depression
  - Fewer depressive symptoms in Speed training
  - Subjects in Memory & Reasoning Training with depressive symptoms profit from training

- Health-Related Quality of Life (HRQoL)
  - Less decline in HRQoL in Memory, Reasoning, & Speed training
Dementia findings: 10-yr follow-up

N=2785 participants in analyses, n=296 met dementia criteria (10.6%)

*Edwards et al. (2016), AAIC*
Speed training delays dementia onset

HR = 0.67, 95% CI 0.49 - 0.91, p = .012

33% risk reduction
Effects of speed training are dose dependent

$HR=0.52, \ 95\%CI \ 0.33-0.82, \ p=0.005$

48% risk reduction
Cognitive Reserve
Clinical Expression of Neurologic Disease

- Not everyone with Alzheimer’s Disease develops dementia
- Alzheimer’s Disease (AD)
  - Persons without clinical dementia can meet post-mortem neuropathological criteria for AD
  - Numerous studies show that lower educational attainment is a risk factor for AD-related dementia.
Cognitive Reserve Hypothesis

Persons with higher lifetime intellectual enrichment can better withstand disease-related neuropathology without suffering cognitive impairment or dementia, likely due to more efficient neurocognitive processing.

Stern et al., *JINS* 2002;8:448-460.
Evidence of Cognitive Reserve in Alzheimer’s Disease

How is Cognitive Reserve Measured?

• Cognitive reserve is a construct. Thus is measured by proxy
  – Years of education
  – Pre-morbid IQ
    • Vocabulary
    • word reading
  – Cognitively-stimulating leisure activity
What about MS?

Cognitive Reserve
Does cognitive reserve moderate the relationship between MS diagnosis and development of cognitive impairment?
Cognitive reserve protects against cognitive dysfunction in multiple sclerosis

James F. Sumowski,1,2 Nancy Chiaravalloti,1,2 and John DeLuca1,2,3

1Kessler Foundation Research Center, Neuropsychology and Neuroscience Laboratory, West Orange, NJ, USA
2UMDNJ–New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ, USA
3UMDNJ–New Jersey Medical School, Department of Neurology and Neurosciences, Newark, NJ, USA
Cognitive Reserve and Cognition in MS

Memory

Cognitive Efficiency

Sumowski et al., 2009, J. Clin Exp Neuropsych
Cognitive Reserve and Brain Imaging

- Brain atrophy predicts Cognition in MS

- Prediction is incomplete:
  - $R^2$s vary between approximately 25 and 45

- Does cognitive reserve moderate the relationship between brain atrophy and cognition in MS?
Intellectual enrichment lessens the effect of brain atrophy on learning and memory in multiple sclerosis

James F. Sumowski, PhD
Glenn R. Wylie, DPhil
Nancy Chiaravalloti, PhD
John DeLuca, PhD

ABSTRACT

Objective: Learning and memory impairments are prevalent among persons with multiple sclerosis (MS); however, such deficits are only weakly associated with MS disease severity (brain atrophy). The cognitive reserve hypothesis states that greater lifetime intellectual enrichment lessens the negative impact of brain disease on cognition, thereby helping to explain the incomplete relation-
Cognitive Reserve in MS

Cognitive Reserve in SPMS

Sumowski et al., 2012, *MSJ*
Benefits of Early Life Cognitive Leisure Activity and Aerobic Exercise in Multiple Sclerosis
Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis

J.F. Sumowski, PhD  
G.R. Wylie, DPhil  
A. Gonnella, EdM  
N. Chiaravalloti, PhD  
J. DeLuca, PhD

ABSTRACT

Objective: Consistent with the cognitive reserve hypothesis, higher education and vocabulary help persons with Alzheimer disease (AD) and multiple sclerosis (MS) better withstand neuropathology before developing cognitive impairment. Also, premorbid cognitive leisure (e.g., reading, hobbies) is an independent source of cognitive reserve for elders with AD, but there is no research on the contribution of leisure activity to cognition in MS. We investigated whether premorbid cognitive leisure protects patients with MS from cognitive impairment.
Leisure Activity Scale

Several leisure activities are listed below. Please read each item and indicate how frequently you performed the activity during your early 20’s before you developed MS. Respond by circling the number that represents your typical participation in each activity during your early 20’s before you developed MS. Only report on activities that were performed for leisure, not activities performed to fulfill educational or occupational requirements. If you are unsure of the exact frequency of your participation, please provide your best estimate. Please circle one number for each item rather than marking between numbers.

**During your early 20’s before you developed MS, how often did you...**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Daily</th>
<th>Several Times per Week</th>
<th>Several Times per Month</th>
<th>Several Times per Year</th>
<th>Once / Less per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read books</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Read magazines or newspapers</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Produce art (e.g., painting, poetry, sculpture, song writing, ballet, etc.)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Produce non-artistic writing (e.g., diary, newsletter, essay, blogs, etc.)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Play a musical instrument</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Play structured games (e.g., cards, board games, crossword puzzles, etc.)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Participate in hobbies (e.g., gardening, model building, web design, etc.)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Results

Cognitive Leisure Activity is positively associated with current cognitive status ($r_p = .49, p < .01$).

Sumowski et al., (2010), Neurology, 75, 1428-1431
Maintenance vs decline in recreational activity since MS diagnosis

Booth et al, 2013, JINS.
Occupation and Cognitive Reserve in MS*

Adjusted for atrophy and IQ

* Adjusted for atrophy and IQ

Gaffer et al 2012, PLOSone
Longitudinal analysis of Cognitive Reserve in MS

Mean Test re-test: 5 years

Cognitive Reserve:
Yrs education
NAART

Benedict et al, 2010, JINS
Cognitive Decline over Time in MS: 4.5 year follow-up

Cognitive Efficiency

- **Baseline**: Blue line, \( \Delta = 0.00 \)
- **Follow-up**: Green line, \( \Delta = -0.63 \)
- **Follow-up**: Red line, \( \Delta = -1.28 \)

Memory

- **Baseline**: Blue line, \( \Delta = -0.24 \)
- **Follow-up**: Green line, \( \Delta = -0.57 \)
- **Follow-up**: Red line, \( \Delta = -0.92 \)

Blue = Hi; Green Mod; Red Low CR

Sumowski et al, submitted
Reserve Concepts and MS

- Higher cognitive reserve protects MS subjects from MS-related cognitive decline

- What about “Brain Reserve”?
Brain Reserve Hypothesis

Persons with larger lifetime brain growth/size (estimated with intracranial volume) can withstand more severe neuropathology without suffering cognitive impairment or dementia.

Persons with larger lifetime brain growth/size have more brain to lose before suffering cognitive decline.

Stern et al., *JINS* 2002;8:448-460.
Results: Brain Reserve

p<.017

Sumowski et al (2013), Neurology
Results: Brain Reserve

Sumowski et al (2013), Neurology
Correlation between Brain Reserve & Cognitive Reserve

Brain size is correlated with education and intelligence
   Witelson et al., *Brain*; 2006;129:386-398
   Deary et al., *Nat Rev Neurosci* 2010;11:201-211

Brain size is genetically determined
   Posthuma et al., *Nat Neurosci* 2002;5:83-84.
   Thompson et al., *Nat Neurosci* 2001;4:1253-1258
   Deary et al., *Nat Rev Neurosci* 2010;11:201-211
QUESTION

Does intellectual enrichment (cognitive reserve) protect MS patients from cognitive impairment independently of maximal lifetime brain size (brain reserve)?

Do people have control over their own destiny?
Results: Cognitive Reserve

p < .001
Results: Cognitive Reserve after factoring out Brain Reserve

Sumowski et al (2013), *Neurology*
Brain Reserve and Cognitive Reserve

- Higher “cognitive reserve” can protect against expression of cognitive impairment in MS over and above the influence of “brain reserve” (larger brain size)
Higher cognitive reserve protects MS subjects from MS-related cognitive decline

Can we identify “at risk” patients?

Can one build up a “cognitive reserve”?  
  - “neuroprotective” against developing cognitive impairment?
The Alzheimer’s Association Website

Keep your brain active every day:
• Stay curious and involved — commit to lifelong learning
• Read, write, work crossword or other puzzles
• Attend lectures and plays
• Enroll in courses at your local adult education center, community college or other community group
• Play games
• Garden
• Try memory exercises
Exercise and Cognition
Exercise and Cognition in MS

- Exercise training may be a behavioral approach for managing cognitive dysfunction in MS, but understudied
- Well-established literature in the general population
- Of the existing MS studies
  - most are not RCTs
  - suffer from significant methodological flaws including
    - small sample sizes
    - poorly-defined interventions
    - lack of adequate control groups
    - inclusion of cognition as a non-primary outcome
- Data in the literature on MS is mixed
Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings

V. M. Leavitt¹,², C. Cirnigliaro³, A. Cohen¹, A. Farag³, M. Brooks³, J. M. Wecht³, G. R. Wylie¹,², N. D. Chiaravalloti¹,², J. DeLuca¹,², and J. F. Sumowski¹,²

¹Kessler Foundation Research Center, West Orange, NJ, USA
²Rutgers – New Jersey Medical School, Newark, NJ, USA
³James J. Peters VA Medical Center, Bronx, NY, USA
⁴Kessler Institute of Rehabilitation, West Orange, NJ, USA

2 RRMS patients randomized to aerobic vs non-aerobic training
30 min sessions, 3x/week for 3 months
## Memory and Aerobic Exercise

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th>Stretching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>+ 16.5%</td>
<td>+ 2.8%</td>
</tr>
<tr>
<td>Cerebral Grey Matter</td>
<td>+ 2.4%</td>
<td>+ 2.9%</td>
</tr>
<tr>
<td>Memory</td>
<td>+ 53.7%</td>
<td>+ 0.0%</td>
</tr>
<tr>
<td>Non-Memory Cognition</td>
<td>+ 0.0%</td>
<td>+ 0.0%</td>
</tr>
</tbody>
</table>

Leavitt et al., *Neurocase*, 2013
Memory and Aerobic Exercise

Leavitt et al., Neurocase, 2013
Treadmill Walking Exercise Training and Brain Function in Multiple Sclerosis: Setting the Stage for a Network-Based Approach to Rehabilitation

Brian M. Sandroff, Ph.D., Glenn R. Wylie, Ph.D., Brad P. Sutton, Ph.D., Curtis L. Johnson, Ph.D., John DeLuca, Ph.D. & Robert W. Motl, Ph.D.

- pilot, single-blind RCT on treadmill walking exercise training intervention on RSFC & cognition
- 8 fully-ambulatory RRMS females randomly assigned into:
  - exercise training intervention (n=5) or waitlist control (n=3)
- 12-weeks of supervised, progressive treadmill walking exercise training
- Pre-post of thalamocortical RSFC
- intervention increased RSFC between thalamus and:
  - right middle frontal gyrus (MFG; d=1.92)
  - anterior cingulate cortex (ACC; d=1.70)
- Intervention improved SDMT performance (d=0.72)
- Change in SDMT associated with RSFC change between thalamus and:
  - right MFG (r=.42)
  - ACC (r=.53)
- Supports exercises as adaptive compensatory mechanism

Sandroff et al, Submitted
RSFC with Thalamus Following Exercise

ACC

Resting-state functional connectivity between thalamus and anterior cingulate cortex

R Middle frontal gyrus

Resting-state functional connectivity between thalamus and right middle frontal gyrus

Sandroff et al, Submitted
Areas in which thalamic RSFC significantly increased following treadmill walking exercise training compared with waitlist control.

Sandroff et al, Submitted
Exercise and Cognition in MS

• Conclusions
  - No conclusive data to support effectiveness
    • Exercise
    • Physical activity
    • Physical fitness
• Future studies
  - Improve methodology
  - Design studies to look specifically at cognition
  - Replication is required
Overall Summary

• Cognitive Reserve and Brain Reserve protect against the negative effects of brain dysfunction in MS
  – Protects against cognitive decline
• Impact of Cognitive Reserve on cognition found over and above impact of Brain Reserve
• Environmental enrichment should be a major focus of rehabilitation on MS
  – Can we build cognitive reserve?
• Exercise may hold promise to improve cognition, but data is preliminary
THANK YOU

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Nancy Chiaravalloti, Ph.D.
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Yael Goverover, Ph.D., OT
Nancy Moore, M.S.
Helen Genova, Ph.D.
Victoria Leavitt, Ph.D.
Ekatrina Dobryakova, Ph.D.
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
An Educational Conference for People with Multiple Sclerosis
Panel Discussion I

Fatigue, Motivation & Physical Activity

Ekaterina Dobryakova, PhD
Helen Genova, PhD
Glenn Wylie, PhD

Moderator: Michele Pignatello
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
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PANEL DISCUSSION II

Wellness, Social Cognition, Everyday Life & Employment

Helen Genova, PhD
Yael Goverover, PhD
Kimberly Beckwith-McGuire, PhD
Lauren Strober, PhD

Moderator: Michele Pignatello
IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH
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REMINDER Podcasts available at:
Kesslerfoundation.org/MS2017

THANK YOU!
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